

TEACHING CASE REPORT

Inappropriate secretion of thyroid-stimulating hormone

The Case: A 39-year-old man presented with fatigue and persistently elevated thyroid-stimulating hormone (TSH), free thyroxine (free T_4) and free triiodothyronine (free T_3) levels. He was euthyroid by symptoms, and he did not report headaches or visual problems. He was not taking any medications, and his medical and family histories were noncontributory. Findings on physical examination revealed a slightly enlarged, nontender thyroid gland but were otherwise unremarkable.

Laboratory investigations revealed a TSH level of 11.9 (normal 0.35–5.0) mU/L, total T_4 level of 154 (normal 63–151) nmol/L, free T_4 level of 20.2 (normal 9–19) pmol/L and free T_3 level of 7.2 (normal 2.63–5.70) pmol/L. A free T_4 level was checked by means of equilibrium dialysis, and it was also elevated, at 27.5 (normal 12–26) pmol/L. The elevated levels of TSH, free T_4 and free T_3 were indicative of inappropriate secretion of TSH, either due to a TSH-secreting pituitary adenoma (TSHoma) or resistance to thyroid hormone. Further investigations were performed to differentiate between the 2 causes. The serum α -subunit level was 1.9 ng/mL (normal < 1.0) ng/mL, and the α -subunit:TSH molar ratio (α -subunit \times 10/TSH) was 1.75 (normal < 1). The TSH level increased to 13.0 mU/L from 7.4 mU/L after administration of thyrotropin-releasing hormone. Genetic analysis for mutation in the thyroid hormone receptor β gene was negative. An MRI scan revealed a 3-mm adenoma in the right side of the pituitary gland (Fig. 1), and the radiolabelled octreotide scan showed somatostatin receptors in the pituitary gland region (Fig. 2).

These biochemical and radiological investigations were consistent with the

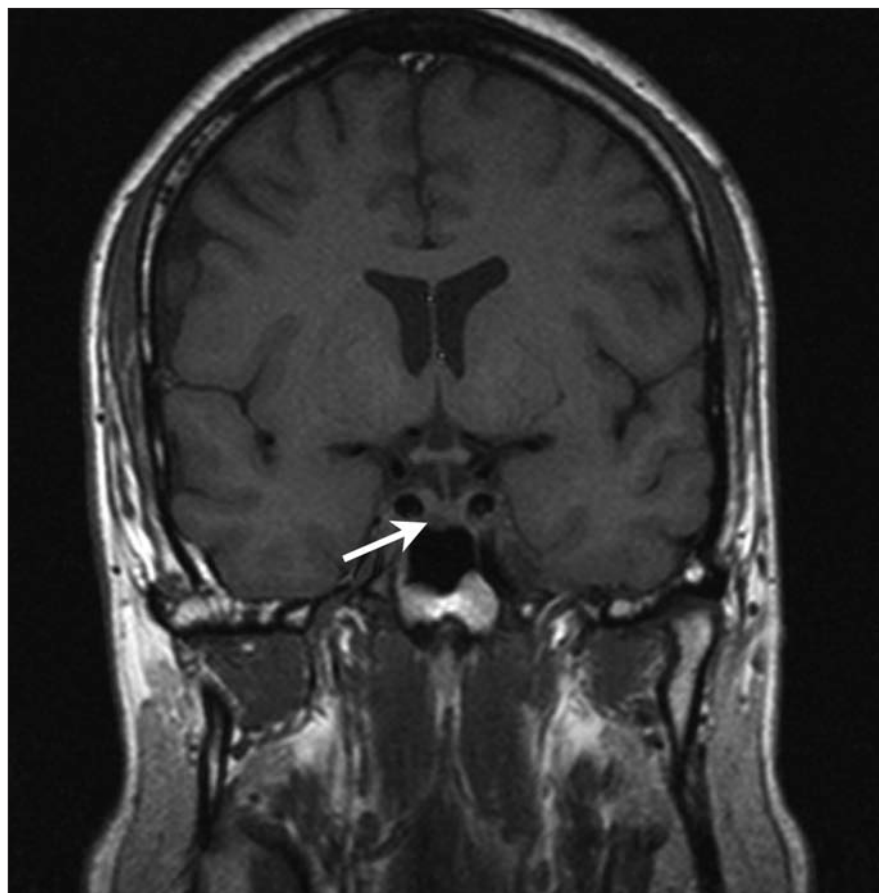


Fig. 1: Small region of hypointensity in the inferior aspect of the right half of the pituitary (arrow), consistent with a microadenoma.

diagnosis of a TSHoma. The patient declined medical or surgical treatment and has remained clinically euthyroid during 4 years of follow-up. His mild biochemical hyperthyroidism and the size of the pituitary adenoma have remained stable.

A majority of patients with hyperthyroidism and elevated T_4 and T_3 levels have undetectable levels of TSH. Uncommonly, hyperthyroid patients may have inappropriately normal or elevated levels of TSH (inappropriate secretion of TSH) that pose a diagnostic dilemma. An adequate review of the patient's history can usually rule out medications or systemic and acute psychiatric illnesses as causes of inappropriate se-

cretion of TSH (Box 1). An increase in thyroxine-binding globulin leading to elevated total T_4 levels can be excluded by measuring the free T_4 and T_3 levels.

Box 1: Causes of inappropriate secretion of thyroid-stimulating hormone (TSH)

- Interfering antibodies to thyroxine (T_4) and triiodothyronine (T_3)
- Amiodarone therapy
- Familial dysalbuminemic hyperthyroxinemia
- L-thyroxine overdose or intermittent L-thyroxine therapy
- Acute psychiatric illness
- TSH-secreting pituitary adenoma
- Resistance to thyroid hormone



Fig. 2: Octreotide scan demonstrating normal physiologic distribution of radioactive isotope along with focus of increased activity in pituitary region (arrow).

Methodologic inaccuracies caused by binding protein abnormalities (e.g., familial dysalbuminemic hyperthyroxinemia) and antibodies to TSH, T_4 or T_3 can be eliminated by using direct “2-step” methods such as equilibrium dialysis.

Two rare but important causes of inappropriate secretion of TSH are TSHomas and resistance to thyroid hormone.¹ Distinguishing between the 2 can pose diagnostic and therapeutic dilemmas. An accurate diagnosis is essential, because delayed diagnosis of TSHomas can lead to tumour growth and poor surgical cure rates, whereas medical, surgical or radioablative treatments in patients with resistance to thyroid hormone are usually unnecessary and potentially harmful.

TSHomas are rare, with a prevalence

Box 2: Clinical manifestations and diagnostic features of TSH-secreting pituitary adenomas (TSHomas) and resistance to thyroid hormone

TSHomas

- Clinically hyperthyroid
- Goiter*
- Headaches*
- Visual-field defects*
- Elevated TSH, T_4 and T_3 levels
- Elevated α -subunit level
- Increased α -subunit:TSH ratio
- Elevated levels of markers of thyroid hormone action (ACE, SHBG)
- < 2-fold increase in TSH level after administration of TRH
- Pituitary adenoma on imaging study
- Positive octreotide scan

Resistance to thyroid hormone

- Clinically euthyroid, hypothyroid or hyperthyroid
- Goiter*
- Developmental delay*
- Hearing loss*
- Elevated TSH, T_4 and T_3 levels
- Normal α -subunit level
- Normal α -subunit:TSH ratio
- Normal levels of markers of thyroid hormone action (ACE, SHBG)
- > 2-fold increase in TSH level after administration of TRH
- Positive mutation in *THRB* gene*
- Negative pituitary imaging study
- Negative octreotide scan

Note: TSH = thyroid-stimulating hormone, T_4 = thyroxine, T_3 = triiodothyronine, ACE = angiotensin-converting enzyme, SHBG = sex-hormone-binding globulin, TRH = thyrotropin-releasing hormone, *THRB* = thyroid hormone receptor beta.

*May or may not be present.

of 1 in 1 million population.² Most patients present with goiter and symptoms of hyperthyroidism, with or without visual disturbances and headaches due to compressive effects of the pituitary macroadenoma. Resistance to thyroid hormone has an incidence of 1 in 50 000 live births and is usually transmitted in an autosomal dominant fashion; however, 15% of cases are sporadic.³ Resistance to thyroid hormone is further classified into 2 major forms: generalized resistance and pituitary resistance. Generalized resistance to thyroid hormone is associated with ubiquitous resistance to thyroid hormone, whereas in pituitary resistance to thyroid hormone, the resistance lies mainly at the level of the pituitary thyrotropes and other tissues remain sensitive to the action of thyroid hormone. Thus, the former is associated with symptoms of hypo- or euthyroidism and the latter with symptoms of thyrotoxicosis.

Given the biochemical similarities between TSHomas and resistance to thyroid hormone, a number of additional investigations are required (Box 2). Peripheral markers of thyroid hormone action, such as sex hormone-binding globulin and angiotensin-converting enzyme levels, are often

elevated in TSHomas but are normal in patients with resistance to thyroid hormone. These levels were normal in our patient. Other tests include measurement of the α -subunit and α -subunit:TSH molar ratio. TSH, follicle-stimulating hormone and leutinizing hormone share a common α -subunit, whereas a distinct β -subunit confers biological specificity. Because α -subunit is cosecreted with TSH from the pituitary gland, elevated levels are suggestive of a TSHoma. However, because α -subunit secretion increases along with leutinizing hormone and follicle-stimulating hormone after menopause, the α -subunit:TSH molar ratio is considered to be a more specific indicator. The thyrotropin-releasing hormone stimulation test is also useful in differentiating between TSHomas and resistance to thyroid hormone. Patients with the latter condition will have a normal or a hypothyroid response, (> 2-fold TSH elevation after administration of thyrotropin-releasing hormone), whereas patients with TSHomas generally have a less than 2-fold elevation of TSH after administration of thyrotropin-releasing hormone, which suggests autonomy of the thyrotropes. In contrast, patients with primary hyperthyroidism (e.g., Graves'

disease) have a flat response to thyrotropin-releasing hormone testing. In a series of 25 patients with TSHomas, it was found that an elevated baseline TSH, flat or decreased response to thyrotropin-releasing hormone and elevated α -subunit or α -subunit:TSH ratio had the highest sensitivity and specificity for diagnosis of TSHomas. A mutation in the thyroid hormone receptor β gene will provide a definitive diagnosis of resistance to thyroid hormone, but in about 10% of cases there are no mutations. Documentation of elevated thyroid hormone levels in asymptomatic family members is also suggestive of resistance to thyroid hormone. The presence of a pituitary adenoma on an MRI scan and somatostatin receptors on the pituitary on a radiolabelled octreotide scan are also compatible with the diagnosis of a TSHoma. However, because as many as 15% of normal people may harbour a small, nonfunctioning pituitary adenoma, patients with resistance to thyroid hormone may have abnormal imaging findings incidentally.

Treatment options for TSHomas include transphenoidal adenomectomy, with or without pituitary irradiation, and medical treatment with somatostatin analogues such as octreotide. Somatostatin analogues may correct the biochemical hyperthyroidism and lead to tumour shrinkage. Treatment of resistance to thyroid hormone involves ensuring that asymptomatic patients do not receive unnecessary hyperthyroid treatment with thionamides, iodine-131 ablation therapy or thyroid surgery. Screening and appropriate diagnosis of family members are also important to avoid therapeutic misadventures. Hypothyroid patients with generalized resistance to thyroid hormone may achieve clinical euthyroidism with very high doses of exogenous thyroid hormone. Clinically hyperthyroid patients with pituitary resistance to thyroid hormone may benefit from treatment with β -blockers and thionamides.

In the case we have described, the findings from the laboratory and radiological investigations were consistent with the diagnosis of a TSHoma. Un-

like most patients with TSHomas, our patient was relatively asymptomatic, had mild biochemical hyperthyroidism and had a fairly small pituitary adenoma. The definitive diagnosis can be obtained only after demonstrating positive TSH immunostaining of pituitary tissue obtained at surgery. Because the patient declined therapeutic intervention, we have elected to continue to provide close clinical, biochemical and radiological monitoring.

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Competing interests: None declared.

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